

**REMARKS****I. Rejections under 35 USC §103(a)**

Claims 1, 2, 5, 7, 11, 13-15 and 18 remain rejected under 35 USC §103(a) as being unpatentable over Denis et al., US Patent No. 5,286,629. The rejection is stated as follows:

Applicants argue that any beneficial effects achieved by the compositions disclosed in the Denis et al patent is achieved by the product to which the ligand is bound and not by the ligand per se, the sole function of which is to get the product to the proper cell. This argument is not persuasive because the ligand (which may be a phosphosugar) is part of the composition that is used to treat skin. The phosphosugar of the Denis et al [*sic*, patent?] as part of the composition that is applied falls within the scope of being a component of a composition that is applied to the skin as instantly claimed. Applicants are reminded that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present....The Denis et al patent clearly shows that the use of a phosphosugar in a composition that can be use in a regimen [*sic*, regimen] to treat damage in skin is well known in the art. The fact that Applicants have found that the composition containing phosphosugar is more effective than anticipated (i.e., can be used to exfoliate skin) is not persuasive of unobviousness where what is claimed would flow naturally from the teachings of the prior art.

The present claims have been amended to identify the phosphosugar employed in the claimed methods as a mannose phosphate, and in a specific embodiment, mannose-6-phosphate. Because of the claim amendment, the subject matter of claims 1, 2, 5, 7, 8, 11 13-15 and 18 have either been canceled or no longer corresponds to that of the corresponding claims, but rather claims 3 and 4, 9 and 10 and 16 and 17. Although the latter claims are addressed more specifically in a subsequent rejection, to the extent the Examiner has made the foregoing statements part of the later rejection, Applicants will address those applicable aspects of the rejection here.

The Examiner's position regarding phosphosugars generally, and mannose-6-phosphate in particular, as it relates to the Denis reference is simply incorrect, both technically and legally. To address the technical errors first, the statement that the Denis reference utilizes "identical chemical compositions" is categorically false. While the treatment compound used in Denis utilizes a phosphosugar as a starting material in making the final active compound, the compound that is actually used is not a phosphosugar *per se* and is unequivocally not chemically identical to a phosphosugar. That derivatizing a compound, by adding a moiety or otherwise modifying its structure, is likely to alter some, if not all properties possessed by the compound being derivatized, is a fact so well known by chemists that it doesn't even bear further discussion. In

the present case, the phosphosugars are derivatized by the addition of various other chemical moieties on to them; indeed, the authors refer to the residues as "osides" and not "oses" as the underivatized compounds would be called. They are no longer phosphosugars as claimed in the present claims. Clearly then, on that basis alone, the reference does not utilize in treatment "identical" compounds to the present invention; if the Examiner truly believes that, for example, the BSA molecule containing phosphogalactoside residues is the "identical" chemical entity to galactose-6-phosphate, and that these two molecules possess "identical" properties, then the Examiner is respectfully requested to provide the technical basis for this position, because it is, quite simply, completely contrary to the basic tenets of chemistry. Because this position is technically untenable, this alone defeats the basis of the rejection.

However, the rejection also fails on legal grounds. The Examiner asserts that the Denis document shows that phosphosugars can be used in a regimen to treat damaged skin. However, this is an overly expansive view of what Applicants are claiming. None of Applicants' claims are directed so broadly as "treatment of damaged skin", and conversely, none of the disclosures of the use of the Denis compounds relate to the use of these compounds in exfoliation. The Examiner's assertion that exfoliation is simply a "more effective" method of treating damaged skin than disclosed in Denis simply confirms Applicants' position that the use of phosphosugars for exfoliation or in increasing glycosaminoglycans is not disclosed in Denis. Moreover, the Denis reference does not disclose any amount of phosphosugars that is effective in either treating damaged skin, or in exfoliation or in increasing glycosaminoglycans, because the reference does not disclose contemplating using these materials in treatment. If the Examiner can show where is a disclosure in Denis as to "effective amounts" of phosphosugars for treatment of any condition, let alone those of the present invention, it is respectfully requested that this be pointed out. In the absence of some clear teaching of the amount, or the treatment of the claimed conditions, the Examiner cannot assert that the disclosure inherently teaches an amount effective to treat the conditions. For the foregoing reasons, therefore, the analysis of the Denis reference is fatally flawed, and cannot provide the basis for any rejection based on this patent.

Claims 3, 4, 6, 9, 10, 12, 16, 17 and 19 remain rejected under 35 USC §103(a) as being unpatentable over Denis et al as applied above, and further in view of Ferguson, US Patent No. 5,520,926. The rejection states as follows:

In response to applicant's argument that a rejection of the claims over the Denis et al. patent further in view of Ferguson patent would only arrive at the conclusion that mannose phosphates could be used as ligands to deliver therapeutic products to the skin, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious....Applicants further argue that Ferguson

indicate that mannose phosphates are not equivalent to galactose-6-phosphate and therefore one skilled in the art would not substitute the mannose phosphates of Ferguson for the galactose-6-phosphate named by Denis et al, to achieve the methods of the present invention. This argument is not persuasive since the Denis et al. and Ferguson patents establish that compositions comprising phosphosugars to treat damaged skin is well known in the art.

The Examiner is again incorrect on both a technical and legal basis. First, as noted above, the Examiner is on shaky legal ground in not examining the claims for the specifics of what is claimed, and rather relies on a broad interpretation of Denis as teaching "treatment of damaged skin" and therefore, in this interpretation, precludes the patentability of any therapeutic method involving treatment of skin. Again, Applicants are claiming specific methods of treatment that are nowhere disclosed in Denis, and the Examiner has not provided any basis, other than this poorly founded sweeping and conclusory generalization, for asserting that the claimed methods of exfoliation and increasing glycosaminoglycans are inherently accomplished by the methods of Denis. More importantly however, with respect to the specific application of these rejections to claims directed to the use of mannose phosphates, particularly mannose-6-phosphate, the inadequacies of this rejection are even clearer. Even if one were to assume, *arguendo*, that the interpretation of Denis is correct, it is patently incorrect when applied to the obviousness of the use of mannose-6-phosphate, even when combined with the teachings of Ferguson.

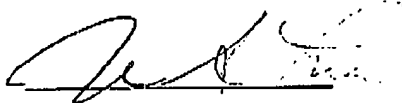
The Examiner is requested to read carefully the disclosure of Denis. This reference teaches very explicitly that only one phosphosugar, specifically galactose-6-phosphate, has the desired properties that are claimed in that document. If attention is turned to Column 1, lines 36-37, of Denis, it is noted that mannose-6-phosphate, the subject of the present claims, is distinguished from the sugars of the Denis claims, in that it is recognized by fibroblasts, which is not the case with galactose-6-phosphate (see column 8, lines 13-15). Therefore, Denis expressly teaches that mannose-6-phosphate is not an equivalent of the single phosphosugar used in the claimed compositions, and also therefore teaches that all phosphosugars, and especially mannose-6-phosphate, cannot be expected to be useful in the methods disclosed therein. On this basis alone, therefore, even if the Denis reference disclosed methods analogous to the ones claimed here, the authors are specifically teaching that a mannose phosphate would not be a good substitute for the galactose-6-phosphate. This alone is enough to demonstrate the complete unobviousness of the use of mannose phosphate in the Denis method. If one looks to the Ferguson disclosure, and combines that disclosure with Denis, one comes to the same conclusion. Ferguson teaches mannose phosphates, and only mannose phosphates confer the desired effect,

wound-healing, which is a completely different utility from that claimed herein. Ferguson also discloses, in column 3, lines 18-19, that galactose-6-phosphate is not equivalent in activity to mannose phosphates. To the extent the Examiner relies on Denis for disclosure of the present methods, however spurious that reliance may be, in view of the disclosure in both references, that mannose phosphate is not equivalent to galactose-6-phosphate, no person skilled in the art would read these references and even be led to combine their teachings, let alone be led to substitute a mannose phosphate for the galactose-6-phosphate of Denis. Therefore, in summary, the Examiner's statement that both references teach "phosphosugars" in the broad sense as being useful in treating damaged skin is overbroad and essentially inaccurate. One reference teaches that only galactose-6-phosphate is useful in its disclosed method, and the other teaches that only that mannose-6- or mannose-1-phosphates are useful in its disclosed method. Each teaches that the specific phosphosugars disclosed are not equivalent to the other, and further, neither discloses the specific methods claimed herein. In view of this abundance of evidence, it is clear that the rejection of the present claims, as amended to be directed to the use of mannose phosphates, is without any legal or technical foundation, and therefore must be withdrawn.

#### CONCLUSION

The present claims are believed to be in condition for allowance, and prompt issuance of a Notice of Allowance is respectfully solicited. The Examiner is encouraged to contact the undersigned by telephone if it is believed that discussion will resolve any outstanding issues.

Respectfully submitted,



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